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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/982,531	10/19/2001	Astrid Vrang	54320.000011	8179

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EXAMINER	
VOGEL, NANCY S	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/982,531	VRANG ET AL.	
	Examiner	Art Unit	
	Nancy T. Vogel	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,14,17,24,27 and 30-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,14,17,24,27 and 30-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-11, 14, 17, 24, 27, 30-45 are pending in the case.

The following are new grounds of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-10, 14, 17, 24, 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Madsen et al. (WO 98/10079) (cited by applicants) in view of Callewaert et al. (Appl. Environ. Microbiol., 66, 2, 606-612, 2000), and Jensen et al. (Appl. And Environ. Microbiol., 59 (12), 4363-4366, 1993).

Madsen et al. disclose a method of producing a heterologous polypeptide in a lactic acid bacterium comprising constructing a recombinant lactic acid bacterium comprising a nucleotide sequence coding for the heterologous polypeptide and operably linked thereto, appropriate regulatory nucleic sequences to control the expression of the coding sequence, cultivating said recombinant bacterium under fed-batch cultivation conditions in a chemically defined medium to express the gene, and harvesting the recombinant bacterium or the polypeptide (see claims, see pages 6 line 12 – page 8, line 15). The promoter may be regulatable, including regulation by accumulation of a metabolite intracellularly or in the medium (see page 6, lines 17-28). The lactic acid bacterium may include a signal peptide operably linked to the nucleotide sequence (see page 12 , line 19 – page 13, line 2). The reference discloses that chemically defined media may be used, and levels up to and exceeding 30 mg/L may be obtained (see page 70, lines 1-17 and page 72, lines 14-25).

The difference between the reference and the claims is that specific media components, including glucose, and controlled feeding of glucose in fed-batch or continuous culture, are recited.

However, Callewaert et al. disclose the growth of lactic acid bacteria in fed-batch culture fermentation, with controlled feeding of glucose dependent on the pH control, for the maximal production of a protein (see page 606-607, end of first column). Jensen et al. disclose minimal growth medium for the growth of Lactococcus lactis bacterium, including genetically engineered strains, which comprises glucose, and which comprises the components listed in claims 24 and 27 (see Table 1), and discloses the

usefulness of said medium when a well-defined growth medium is required (page 4363, first column). The reference discloses that the concentrations of the components of the medium, including glucose, could be increased (see page 4365, first paragraph).

.It would have been obvious to one of ordinary skill in the art to have modified the growth medium for lactic acid bacteria, disclosed by Madsen et al., to use the growth medium and techniques disclosed by Callewaert and Jensen et al., since all of the references are concerned with the maximization of the growth of lactic acid bacteria, including those used for genetic engineering purposes or protein production purposes. One would have been motivated to do so by the disclosure of Jensen et al., that the disclosed media is useful when a well-defined growth medium is required, and the disclosure of Callewaert, that cell growth and protein production can be maximized using conditions such as controlled glucose feeding in fed-batch fermentation. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1-10, 14, 17, 24, 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Madsen et al. (WO 98/10079) (cited by applicants) in view of Callewaert et al. and Jensen et al. (Appl. And Environ. Microbiol., 59 (12), 4363-4366, 1993), and further in view of de Vos (Curr. Opin. 2 (3); 289-295, 1999).

Madsen et al., Callewaert et al., and Jensen et al. are cited for the reasons set forth above.

The difference between the references and the instant claims is that a constitutive promoter is utilized.

However, de Vos disclose the use of constitutive promoters for the expression of genes in lactic acid bacteria (see page 289, second column, line 15 – page 290, second paragraph, line 9).

It would have been obvious to one of ordinary skill in the art, to have utilized a constitutive promoter as taught by deVos, in the method of producing heterologous protein disclosed by Madsen, et al. in view of Callewaert et al., and Jensen, since the references disclose methods of expression of genes in lactic acid bacteria, including the use of promoters operably linked to a gene encoding a polypeptide whose expression is desired. One would have been motivated to do so by the well known properties of constitutive promoters, which include unregulated high levels of production of an operably linked gene of interest, as disclosed by de Vos. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 1-11, 14, 17, 24 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Madsen et al. in view of Callewaert et al. and Jensen et al., and further in view of van Asseldonk et al. (J. Bacteriol., 175, 6, 1637-1644, 1993).

Madsen et al. and Jensen et al. are cited for the reasons set forth above.

The difference between the references and the instant claim is that a particular signal peptide, i.e. the usp45 is utilized.

However, van Asseldonk et al. disclose the usp45 signal peptide, and its use in the production of a protein in L. lactis (see abstract, . It would have been obvious to one of ordinary skill in the art, to have utilized a known L. lactis signal peptide such as the usp45 signal peptide, in the method of producing heterologous protein disclosed by Madsen et al. and Jensen et al., since both references disclose methods of expression of genes in lactic acid bacteria, including the use of signal peptides operably linked to a gene encoding a polypeptide whose expression is desired. It is noted that Madsen et al. disclose at page 12-13, that a signal peptide may be used for the secretion of any protein of interest. One would have been motivated to do so by the well known property of the usp45 signal peptide in directing the secretion of a heterologous protein from a lactic acid bacteria, as disclosed by van Asseldonk et al.

Claims 30, 32-39, 41-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Madsen et al. (WO 98/10079) in view of Callewaert et al. (Appl. Environ. Microbiol., 66, 2, 606-612, 2000), and Jensen et al. (Appl. And Environ. Microbiol., 59 (12), 4363-4366, 1993), and further in view of Israelsen et al. (Appl. Environment. Microbiol., 61(7): 2540-2547, 1995) (cited by applicants).

Madsen et al. disclose a method of producing a heterologous polypeptide in a lactic acid bacterium comprising constructing a recombinant lactic acid bacterium comprising a nucleotide sequence coding for the heterologous polypeptide and operably linked thereto, appropriate regulatory nucleic sequences to control the expression of the coding sequence, cultivating said recombinant bacterium under fed-batch cultivation conditions in a chemically defined medium to express the gene, and harvesting the recombinant bacterium or the polypeptide (see claims, see pages 6 line 12 – page 8, line 15). The promoter may be regulatable, including regulation by accumulation of a metabolite intracellularly or in the medium (see page 6, lines 17-28). The lactic acid bacterium may include a signal peptide operably linked to the nucleotide sequence (see page 12 , line 19 – page 13, line 2). The reference discloses that chemically defined media may be used, and levels up to and exceeding 30 mg/L may be obtained (see page 70, lines 1-17 and page 72, lines 14-25).

The difference between the reference and the claims is that specific media components, including glucose and yeast extract, and controlled feeding of glucose in fed-batch or continuous culture, are recited.

However, Callewaert et al. disclose the growth of lactic acid bacteria in fed-batch culture fermentation, with controlled feeding of glucose dependent on the pH control, for the maximal production of a protein (see page 606-607, end of first column). Jensen et al. disclose minimal growth medium for the growth of Lactococcus lactis bacterium, including genetically engineered strains, which comprises glucose, and which comprises the components listed in claims 24 and 27 (see Table 1), and

discloses the usefulness of said medium when a well-defined growth medium is required (page 4363, first column). The reference discloses that the concentrations of the components of the medium, including glucose, could be increased (see page 4365, first paragraph). However, Israelsen et al. disclose a method of producing a heterologous protein using recombinant lactic acid bacteria (L. lactis), in which the culture medium is supplemented with yeast extract and glucose, i.e. that contained in M17 medium (see page 2540, right column, Materials and Methods).

It would have been obvious to one of ordinary skill in the art to have modified the growth medium for lactic acid bacteria, disclosed by Madsen et al., to use the growth medium and techniques disclosed by Callewaert and Jensen et al., since all of the references are concerned with the maximization of the growth of lactic acid bacteria, including those used for genetic engineering purposes or protein production purposes. One would have been motivated to do so by the disclosure of Jensen et al., that the disclosed media is useful when a well-defined growth medium is required, and the disclosure of Callewaert, that cell growth and protein production can be maximized using conditions such as controlled glucose feeding in fed-batch fermentation. It would have been further obvious to one of ordinary skill in the art to have used yeast extract and glucose in a culture medium for growth of lactic acid bacteria, as taught by Israelsen et al., since both Madsen et al., Jensen et al., Callewaert et al. and Israelsen et al. disclose culture methods for growing lactic acid bacteria, for the production of a h protein. One would have been motivated to do so by the well known advantages of using growth medium containing yeast extract, which include the ability to cultivate to

high levels lactic acid bacteria such as L. lactis, as disclosed by the references. It is noted that M17 medium, which contains yeast extract, is a standard medium for growth of lactic acid bacteria, as taught by the reference. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 30-39 and 41-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Madsen et al. (WO 98/10079) (cited by applicants) in view of Jensen et al. (Appl. And Environ. Microbiol., 59 (12), 4363-4366, 1993), Callewaert et al., and Israelsen et al., , and further in view of de Vos (Curr. Opin. 2 (3); 289-295, 1999).

Madsen et al., Callewaert et al., Jensen et al. and Israelsen et al. are cited for the reasons set forth above.

The difference between the references and the instant claims is that a constitutive promoter is utilized.

However, de Vos disclose the use of constitutive promoters for the expression of genes in lactic acid bacteria (see page 289, second column, line 15 – page 290, second paragraph, line 9).

It would have been obvious to one of ordinary skill in the art, to have utilized a constitutive promoter as taught by deVos, in the method of producing heterologous protein disclosed by Madsen, et al. in view of Jensen and Israelsen, since the

references disclose methods of expression of genes in lactic acid bacteria, including the use of promoters operably linked to a gene encoding a polypeptide whose expression is desired. One would have been motivated to do so by the well known properties of constitutive promoters, which include unregulated high levels of production of an operably linked gene of interest, as disclosed by de Vos. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 30-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Madsen et al. in view of Callewaert et al., Jensen et al. and Israelsen et al., and further in view of van Asseldonk et al. (J. Bacteriol., 175, 6, 1637-1644, 1993).

Madsen et al., Callewaert et al., Jensen et al. and Israelsen et al., are cited for the reasons set forth above.

The difference between the references and the instant claim is that a particular signal peptide, i.e. the usp45 is utilized.

However, van Asseldonk et al. disclose the usp45 signal peptide, and its use in the production of a protein in L. lactis (see abstract, . It would have been obvious to one of ordinary skill in the art, to have utilized a known L. lactis signal peptide such as the usp45 signal peptide, in the method of producing heterologous protein disclosed by Madsen et al. and Jensen et al., since both references disclose methods of expression of genes in lactic acid bacteria, including the use of signal peptides operably linked to a

gene encoding a polypeptide whose expression is desired. It is noted that Madsen et al. disclose at page 12-13, that a signal peptide may be used for the secretion of any protein of interest. One would have been motivated to do so by the well known property of the usp45 signal peptide in directing the secretion of a heterologous protein from a lactic acid bacteria, as disclosed by van Asseldonk et al.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6 and 35 are vague and indefinite in the recitation of "or a derivative thereof" since it is not known what the number and types of steps involved in said deriving are. Therefore, the intended metes and bounds of the claimed subject matter cannot be determined.

Response to Arguments

Applicant's arguments with respect to claims 1-11, 14, 17, 24, 27 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy T. Vogel whose telephone number is (571) 272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NANCY VOGEL, PH.D.
PATENT EXAMINER